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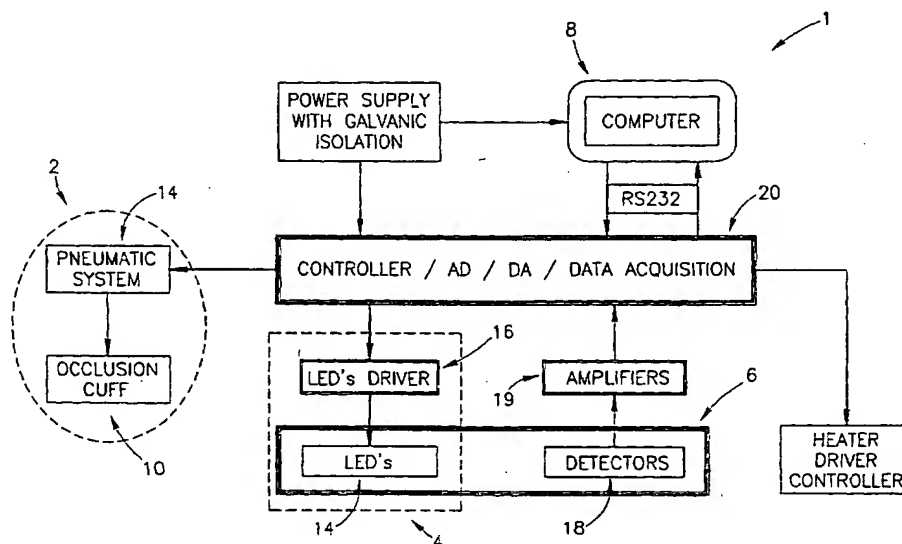
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(54) Title: **A METHOD OF OPTICAL MEASUREMENTS FOR DETERMINING VARIOUS PARAMETERS OF THE PATIENT'S BLOOD**



(57) Abstract: A method for optical measurements of desired parameters of the patient's blood is presented. A state of the blood flow cessation is provided within a measurement region and maintained during a predetermined time period. Measurement sessions are performed within this predetermined time period. Each measurement session includes at least two measurements with different wavelengths of incident light. Obtained measured data is representative of the time dependence of light response of the blood in the measurement region. The analyses of the measured data enables the determination of the desired blood parameters extracted from optical characteristics associated with the erythrocytes aggregation process during the state of the blood flow cessation.

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According to the DC measurement technique, any desired location of a blood perfused tissue is illuminated by the light of a predetermined spectral range, and the tissue reflection and/or transmission effect is studied. Although this technique provides a relatively high signal-to-noise ratio, as compared to the AC measurement technique, the results of such measurements depend on all the spectrally active components of the tissue (i.e. skin, blood, muscles, fat, etc.), and therefore need to be further processed to separate the "blood signals" from the detected signals. Moreover, proportions of the known components vary from person to person and from time to time. To resolve this problem, calibration must periodically be provided, which constitutes an invasive blood test and therefore renders the DC technique of optical measurements to be actually invasive.

The AC measurement technique focuses on measuring only the "blood signal" of a blood perfused tissue illuminated by a predetermined range of wavelengths. To this end, what is actually measured is a time-dependent component only of the total light reflection or light transmission signal obtained from the tissue. A typical example of the AC measurement technique is the known method of pulse oximetry, wherein a pulsatile component of the optical signal obtained from a blood perfused tissue is utilized for determining arterial blood oxygen saturation. In other words, the difference in light absorption of the tissue measured during the systole and the diastole is considered to be caused by blood that is pumped into the tissue during the systole phase from arterial vessels, and therefore has the same oxygen saturation as in the central arterial vessels.

The major drawback of the AC measurement technique is its relatively low signal-to-noise ratio, especially in cases where an individual has a poor cardiac output, insufficient for providing a pulsatile signal suitable for accurate measurements.

Various methods have been suggested to enhance the natural pulsatile signal of an individual for effecting non-invasive optical measurements, and are disclosed for example in the following patents: US 4,883,055; US 4,927,264; and US 5,638,816. All these techniques utilize the artificially induced volumetric changes

characteristics (i.e., absorption and/or scattering) of a blood perfused medium dramatically changes when a character of blood flow changes. It has been found by the inventors, that the optical characteristics of a blood perfused fleshy medium (e.g., the patient's finger) start to change in time, when causing blood flow
5 cessation. In other words, once the blood flow cessation state is established, the optical characteristics start to change dramatically, such that they differ from those of the fleshy medium with a normal blood flow by about 25 to 45%, and sometimes even by 60 %. Hence, the accuracy (i.e., signal-to-noise ratio) of the optical measurements can be substantially improved by performing at least two timely
10 separated measurement sessions, each including at least two measurements with different wavelengths of incident radiation.

The main idea of the present invention is based on the investigation that the changes of the light response of a blood perfused fleshy medium at the state of the blood flow cessation (either monotonous or not, depending on the wavelength of
15 incident radiation) are caused by the changes of the shape and average size of the scattering centers in the medium, i.e., red blood cells (RBC) aggregation (Rouleaux effect). The main principles of this effect are disclosed, for example, in the article "Quantitative Evaluation of the Rate of Rouleaux Formation of Erythrocytes by Measuring Light Reflection ("Syllectometry")", R. Brinkman et al., 1963.

20 At the state of the blood flow cessation, when there is actually no blood flow, no shear forces prevent the erythrocytes' aggregation process. Hence, the light response (transmission) of the blood perfused fleshy medium undergoing the occlusion, which causes the blood flow cessation, can be considered as the time dependence of scattering in a system with growing scatterers.

25 Generally, light response of a medium is defined by the scattering and absorption properties of the medium. According to the model of the present invention, at the state of blood flow cessation under proper conditions, the crucial parameter defining the time evolution of the light response is a number of erythrocytes in aggregates. Therefore, it can be concluded that the average size of
30 aggregates also changes with time. The scattering properties of blood depend on

1500-1600nm may be added to the above-mentioned range of 600-1300nm for selecting the two wavelengths, respectively.

Having determined the parametric slope for a specific patient, a corresponding calibration curve presenting the corresponding parametric slope as the function of the desired parameter is used for determining the desired parameter for the specific patient. The calibration curve, or a set of such curves for different parameters, is previously prepared and stored as reference data. The calibration curve is prepared by applying measurements of the present invention and the conventional ones to different patients, and determining the parametric slope and the desired parameter, respectively. For the determination of oxygen saturation, generally, a calibration curve may be prepared by applying measurements of the present invention to a specific patient, but at the multiple-occlusion mode at the blood flow cessation state in a breath hold experiment.

Additionally, it was found that for one wavelength of the incident radiation the time dependence of transmission signal, i.e., $T(t)$, asymptotically falls, and for the another wavelength it grows. This fact allows for constructing a certain rouleaux geometry factor (RGF). This RGF essentially involves the different time evolutions of light responses at the different wavelengths of incident radiation, and may serve as one of the key-parameters for attributing the measurement results to the certain calibration curve.

The RGF may be constructed in different ways. For example, the RGF can be taken as a certain "cut-off" wavelength λ_0 corresponding to the transmission value staying nearly constant with time. This cut-off wavelength can be determined as the wavelength corresponding to the condition $\Delta T/\Delta t=0$ (or $\Delta(\log T)/\Delta t=0$). On the other hand, it is known from literature and is theoretically obtainable, that a function $K(x(n_{Hb}-n_{pl}))$, which describes the effects of light diffraction on particles depending on the model used, has several extremum values. Here, $x=2\pi a/\lambda$, a being the erythrocyte size; n_{Hb} is the refraction index of hemoglobin and n_{pl} is the refraction index of liquid surroundings, i.e., plasma, which is similar to water by its optical characteristics. It is also known, and is shown in the description below, that

certain blood parameter. This enables to obtain more precise information about the patient's blood.

Generally speaking, the present invention presents a technique for obtaining and analyzing the time changes of the spectral dependence of the light response (transmission) of the patient's blood at the state of blood flow cessation, wherein these changes result from the effect of scattering on particles of different size (erythrocyte aggregates). The state of blood flow cessation is preferably obtained *in vivo* by applying over-systolic pressure to the patient's blood perfused fleshy medium, e.g., his finger, but can also be obtained *in vitro*, by providing the flow of the patient's blood sample into a cuvette and occluding the flow for a certain time period.

For the calculation of the optical properties of blood (reflection and transmission coefficients), properties of the entire system should be connected with the scattering and absorption properties of the unit of the system volume. To this end, the scattering and absorption coefficients are evaluated. As indicated above, for blood, the absorption coefficient μ_{abs} does not depend on the shape of particles and their sizes. What does depend on the particle size is the scattering coefficient μ_{scat} . This conclusion is true for various models of multiple scattering theories, such as the model of Twersky, diffusion models, model of Hemenger, model of Rogozkin, and Small-Angle model.

There is thus provided according to one aspect of the present invention, a method of optical measurements of at least one desired parameter of a patient's blood, the method comprising the steps of:

- providing a state of blood flow cessation of the patient's blood within a measurement region, and maintaining the blood-flow cessation state during a predetermined time period;
- performing measurement sessions within said predetermined time period, each measurement session including at least two measurements with different wavelengths of incident light, and obtaining measured

Alternatively or additionally, the analysis of the measured data includes the determination of an RGF. The term "RGF" used herein is a factor characterizing the light response of blood in the state of blood flow cessation as the function of time and wavelengths of incident radiation, associated with the Rouleaux effect, or erythrocytes' aggregation. In this case, the theoretical data indicative of a scattering function $K(x(n_{Hb}-n_{pl}))$ may be used for determining the parameter $x(n_{Hb}-n_{pl})$ for the specific patient, if the "cut-off" wavelength serves as the RGF. To this end, preferably more than two different wavelengths of incident radiation are used in each measurement session and corresponding time variations of the transmission signals $T(t)$ are measured in order to construct the proper RGF. Then, in the example of the cut-off wavelength, a ratio $\Delta(\log T)/\Delta t$ (or $\Delta T/\Delta t$) as the function of the wavelength λ is determined for the time interval Δt that lies substantially within the asymptotic time interval. The point λ_0 corresponding to the condition $\Delta(\log T)/\Delta t=0$ is the cut-off wavelength of incident radiation corresponding to a certain time stable transmission for a specific patient, which, in turn, corresponds to the extremum of the function $K(x(n_{Hb}-n_{pl}))$, within the accepted range of $(x(n_{Hb}-n_{pl}))$.

Another important parameter that can be obtained through the analysis of the measured data is the EAR, which is determined as the ratio $\Delta T/\Delta t$ or $\Delta(\log T)/\Delta t$. Generally, the use of only one wavelength of incident radiation is sufficient for this specific application. But practically, in order to enable the determination of several different parameters through the single measurement procedure, more than one wavelength is used.

According to another broad aspect of the present invention, there is provided a method of optical measurements of desired parameters of a patient's blood extracted from optical characteristics associated with erythrocytes aggregation process during the state of the blood flow cessation, the method comprising the steps of:

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- analyzing the measured data for determining a Rouleaux Geometry Factor (RGF) for the specific patient, the RGF characterizing the changes of the light response of blood at the state of the blood flow cessation as the function of time and wavelengths of the incident radiation, associated with the erythrocytes' aggregation.

According to yet another aspect of the present invention, there is provided a method of optical measurements of at least one desired parameter of blood of a specific patient extracted from optical characteristics associated with erythrocytes aggregation process during the state of blood flow cessation, the method comprising the steps of:

- providing reference data in the form of at least one calibration curve corresponding to a parametric slope as a function of values of said desired parameter;
- providing the state of the blood flow cessation within a measurement region, and maintaining the blood-flow cessation state during a predetermined time period;
- performing timely separated measurement sessions within said predetermined time period, each measurement session including at least two measurements with different wavelengths of incident light, and obtaining the time dependence of transmission signals, wherein the at least two wavelengths are selected in accordance with the desired parameter to be determined;
- analyzing the obtained data for determining the parametric slope value for said specific patient;
- using said calibration curve for determining the value of said desired parameter for said specific patient.

There is also provided a measurement apparatus for performing non-invasive optical measurements of desired parameters of the patient's blood.

data from the graphs in Fig. 3a, and Fig. 6b illustrates a calibration curve in the form of the parametric slope as the function of the concentration of hemoglobin.

Figs. 7a and 7b illustrate the determination of the glucose concentration, wherein Fig. 7a shows the measurement data in the form of transmission signals as the functions of time $T_1(t)$ and $T_2(t)$ for two different wavelengths λ_1 and λ_2 of incident radiation, and Fig. 7b shows a parametric slope plotted as the transmission logarithm at the wavelength λ_2 , i.e., $\text{Log}(T_2)$, versus the transmission logarithm at the wavelength λ_1 , i.e., $\text{Log}(T_1)$;

Figs. 8a to 8c illustrate the determination of the oxygen saturation parameter, wherein Fig. 8a shows two graphs for parametric slopes corresponding to two different pairs of wavelengths, respectively, and Figs. 8b and 8c illustrate one possible example for plotting a corresponding calibration curve;

Figs. 9a and 9b illustrate some more features of the present invention relating to a so-called "MegaSlope" concept, wherein Fig. 9a graphically shows the MegaSlope graph plotted using the measured data of Fig. 3a, and Fig. 9b shows the corresponding calibration curve; and

Fig. 10 illustrates the determination of Erythrocyte Aggregation Rate, showing $\Delta(\log T)/\Delta t$ as the function of Erythrocyte Sedimentation Rate, obtained through the conventional *in vitro* measurements.

20 DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

A method according to the present invention consists of applying optical measurements to the patient's blood while in the state of blood flow cessation, within a measurement region, by irradiating this region with at least two different wavelengths in the near IR or visible range, and detecting transmission signals as the functions of time during a predetermined time period. This can be implemented by applying over-systolic pressure to a location on the patient's organ so as to create the state of blood flow cessation, and applying the optical measurements to a location on the finger downstream of the pressurized location with respect to the direction of a normal blood flow (*in vivo*). Alternatively, the flow of a blood sample

pressurizing assembly). Generally speaking, the control unit 8 is a computer device having such known utilities as a memory, a processor, a synchronizer, a display, etc. The processor is preprogrammed by suitable software capable of analyzing the received output of the detection assembly and determining one or more desired
5 conditions of the patient's blood, as will be described more specifically further below.

Fig. 1b illustrates a measurement apparatus 100 utilized for carrying out a method of the present invention in an invasive manner. To facilitate understanding, the same reference numbers are used for identifying those components which are
10 identical in the apparatuses 1 and 100. The apparatus 100 is generally similar to the apparatus 1, having the same illumination and detection assemblies 4 and 6 and the control unit 8. Here, in distinction to the apparatus 1, a pump 102 serves for directing the flow of the patient's blood sample from a buffer 103 into a cuvette 102. By manipulating the pump, the state of blood flow cessation in the cuvette can
15 be provided and maintained for a predetermined period of time.

Fig. 2 illustrates a graph G presenting experimental results obtained by applying the apparatuses 1 to the patient's blood perfused fleshy medium. The graph G shows how the light-transmitting characteristic of blood changes under the application of the over-systolic pressure. The transmitting characteristic are shown
20 here as the so-called "Relative Transmission", i.e., in Transmission Arbitrary Units or T(A.U.).

The application of pressure starts at a moment T_{start} , and is maintained for a period of time such as not to cause irreversible changes in the fleshy medium (e.g., 4 seconds). The pressure is released at the moment $T_{release}$. Measurements of the
25 Relative Transmission are performed continuously, starting prior to the application of the over-systolic pressure. Different states of the blood flow, designated A, B, C, D and E, are observed. State A is a state of normal blood flow before the over-systolic pressure is applied. As shown, this state is characterized by a standard fluctuating value of the relative light transmission of blood. State B starts at the
30 moment T_{start} (when the pressure is initially applied) and exists during a short

signals, i.e., $T_1(t)$, $T_2(t)$ and $T_3(t)$, corresponding to the wavelengths λ_1 , λ_2 and λ_3 , respectively, obtained with the apparatus 1 (*in vivo*). As shown, the transmission always grows during a certain initial time interval t_{in} , which is different for different wavelengths of incident radiation, and then, in an asymptotic time interval, t_{asym} , it monotonously grows or falls, depending on the wavelength of the incident radiation. Fig. 3b illustrates three graphs corresponding to the time dependence of the transmission signals $T'_1(t)$, $T'_2(t)$ and $T'_3(t)$ obtained with the same three wavelengths, but *in vitro*, i.e., with the measurement apparatus 100 illustrated in Fig. 1b.

As shown, the corresponding graphs in Figs. 3a and 3b, i.e., T_1 and T'_1 , T_2 and T'_2 , and T_3 and T'_3 , are similar. This signifies that the same process takes place in the blood while in the patient's body under the occlusion mode, and in the blood sample in the cuvette, affecting the light response of the blood. This process is the erythrocytes' aggregation.

Turning back to Fig. 2, such an essential difference between the optical characteristics of the blood perfused fleshy medium at the state of blood flow cessation (state C) and those of the fleshy medium with normal blood flow (states A and E) can be explained by the physical and physiological mechanisms - the preferred orientation of red blood cells, their aggregation, and condition of blood vessels. Red blood cells are biconcave discoid cells, the alignment of which drastically changes with the blood flow changes. In turn, scattering properties of the discoid red cells depend on their orientation relatively to the axis of optical measurement. Changes in the scattering properties of the red blood cells alter light absorption of the blood perfused medium. The cessation of the blood flow causes the massive appearance of the aggregated chains that change the light scattering and light absorption of the blood in the fleshy medium. With regard to the condition of blood vessels, the degree of blood perfusion of the vessels and their dimensions essentially depend on the presence of the arterial blood flow, thus affecting optical characteristics thereof.

erythrocyte depends on the dielectric constant of hemoglobin C_{Hb} , which changes in the interval 30-36g/dl. Correspondingly, the relative dielectric constant n' changes in the interval $1.03 < n' < 1.07$ ($1.37 < n_{Hb} < 1.42$). In the whole interval of variation, there is a condition that: $n_{Hb} - n_{pl} < n_{pl}$. Here, the estimations that $n_{Hb} \approx 1.4$,
 5 $n_{pl} \approx n_{H2O}$ and $n_{Hb} - n_{H2O} = 1.4 - 1.33 = 0.07$ are taken.

The process that takes place at the state of blood cessation is the aggregation of erythrocytes, during which the erythrocytes forms a long chain. The number of erythrocytes in aggregate depends on many parameters, such as hematocrit H , chemical composition of the blood plasma, and of erythrocyte themselves.
 10 Considering that initially the erythrocyte is a concave disk or spheroid having its small size c and the long size a , during the aggregation, the erythrocytes adhere to each other along their long surfaces. If there is aggregation with x erythrocytes, the number of aggregates are N/x . The volume per one aggregate is Vx/N . The volume of one aggregate is V_0x . The part of volume occupied by one aggregate, i.e., the
 15 new hematocrit H' , is as follows:

$$H' = (Vx/N) * (1/V_0x) = (V/N * V_0) = H$$

Hence, within this model, the hematocrit of the system does not change in the
 20 process of aggregation.

With aggregation, the size of a responding (scattering and absorbing) particle increases. Simulating the aggregates by a sphere, the radius of an aggregate is: $r' = rx^{1/3}$, wherein r is the radius of the erythrocyte. In a spheroid, the small size $c' = cx$ or both sizes c and a are increased, so that: $(a')^2 c' = a^2 cx$.

25 The total cross-section σ_{tot} is equal to the sum of the scattering cross-section σ_{scat} and absorption cross-section σ_{abs} , that is:

$$\sigma_{tot} = \sigma_{scat} + \sigma_{abs}$$

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point of the radiation ray with the sphere surface. The parameters x' , x and n' are as follows:

$$x' = \frac{2\pi r n_{pl}}{\lambda}; x = \frac{2\pi r}{\lambda}; n' = \frac{n_{Hb}}{n_{pl}}$$

5 The result is:

$$\sigma_{scat} = 4 \cdot \text{Re } K \cos[-2ix(n_{Hb} - n_{pl})] \cdot \pi r^2$$

For real refraction indices (n_{Hb} , n_{pl}), we have:

10
$$\sigma_{scat} = 2\pi r^2 K[x(n_{Hb} - n_{pl})];$$

wherein

$$K(\omega) = 1 - (\sin(2\omega)/\omega + (\sin(\omega)/\omega)^2);$$

15

$$\omega = x(n_{Hb} - n_{pl}), x = 2\pi r/\lambda.$$

Thus, we defined the function $K(\omega)$ which is graphically illustrated in Fig. 4a. This function describes diffraction effects on particles depending on the model used. As shown, this function has the asymptotic value 1 at $\omega \rightarrow \infty$, in which case $\sigma_{scat} = 2\pi r^2$. The other asymptotic expression at small $\omega \rightarrow 0$, $K(\omega) = \omega^2$, but this contradicts with the WKB approximation. For blood, there is the intermediate case $x \approx 20$ and $\omega \approx 1$.

The function $K(\omega)$ has many maximum and minimum values, the physical sense of which is the interference between the refracted and diffracted waves.

25

The similar approach may be applied to each particular geometry of the center of scattering, such as spheroids with averaged parameters over various orientations, etc.

Fig. 4b illustrates the function $K(\langle\omega\rangle)$. It can be seen from this graph that the scattering coefficient μ_{scat} for spheroids which is proportional to $K(\langle\omega\rangle)$ has the finite limit when one of the sizes c increases to infinity. This limit is determined by the unchanged spheroid size a .

The above equations for the scattering coefficient μ_{scat} are very important for the evaluation of the optical properties of blood, with taking into account the real size and shape of erythrocytes. This also allows the evaluation of the optical properties of erythrocytes when they aggregate one with another.

Turning back to Figs. 3a-3b and Fig. 4a, and keeping in mind that $\omega = (2\pi r/\lambda)(n_{\text{Hb}} - n_{\text{pl}})$, i.e., K is the function of the wavelength λ of the incident radiation, we can conclude the following. Since for one wavelength the transmission signal grows with time in the asymptotic time interval t_{asym} and for the other wavelength it falls, there exists such a wavelength (cut-off wavelength) of incident radiation, which causes no time changes in the transmission signal and which corresponds to the extremum (maximum or minimum) of the function $K(\omega)$. The transmission signal corresponding to the cut-off wavelength of incident radiation will therefore be independent on the erythrocyte aggregation process.

Reference is now made to Figs. 5a and 5b, illustrating the main principles of the determination of the cut-off wavelength as an example of the particular RGF. Fig. 5a shows the results of *in vivo* measurements during prolonged occlusion, in the form of several graphs - six in the present example. Graphs $T_1^{\lambda_1}(t) - T_6^{\lambda_7}(t)$ of the time variation of transmission signals correspond to different values of the wavelengths of incident radiation: $\lambda_1=650\text{nm}$, $\lambda_2=700\text{nm}$, $\lambda_3=760\text{nm}$, $\lambda_4=880\text{nm}$, $\lambda_5=940\text{nm}$ and $\lambda_6=1300\text{nm}$. Fig. 5b shows a graph in the form of a ratio $\Delta(\log T)/\Delta t$ as the function of the wavelength λ obtained from the graphs in Fig. 5a, wherein Δt lies substantially within the asymptotic time interval t_{asym} , where the transmission signals change with time slower than in the initial time interval t_{in} . The point λ_0 is

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Since there is a concrete geometry of erythrocytes in the system, the role of their spherical shape in the absorption of radiation should be considered.

The absorption coefficient is expressed by the imaginary part of the refraction indices and is as follows:

5

$$\sigma_{abs} = 2 \cdot \text{Re} \int dS (1 - e^{-4x(s \cdot \text{Im } n_{Hb} + (1-s) \cdot \text{Im } n_{pl}) \cdot \cos \gamma}) = 2 \cdot Kcom(4x(s \cdot \text{Im } n_{Hb} + (1-s) \cdot \text{Im } n))$$

wherein hemoglobin occupies only the part s of the erythrocyte volume V_0 .

For the real system $x \approx 18$, $\text{Im } n_{Hb}, n_{pl}$ is about 10^{-4} and the argument of function is small. Considering the expression for $Kcom[y]$:

10

$$Kcom[y] = \frac{y}{3} - \frac{y^2}{8} + \frac{y^3}{30} + \dots$$

we have:

$$\sigma_{abs} = \frac{8}{3} x \cdot \pi r^2 \cdot (s \cdot \text{Im } n_{Hb} + (1-s) \cdot \text{Im } n_{pl})$$

Taking into account the following:

$$\begin{aligned} 2 \cdot (2\pi / \lambda) \cdot s \cdot \text{Im } n_{Hb} &= \mu_{abs}^{Hb} \cdot C_{Hb} \\ 2 \cdot (2\pi / \lambda) \cdot (1-s) \cdot \text{Im } n_{pl} &= \mu_{abs}^{pl} \cdot (1-s) \cdot \rho_{pl} \\ \frac{4\pi}{3} \cdot r^3 &= V_0 \end{aligned}$$

15

we receive:

$$\sigma_{abs} = (\mu_a^{Hb} \cdot C_{Hb} + \mu_a^{pl} \cdot (1-s) \cdot \rho_{pl}) V_0$$

For the absorption coefficient of erythrocyte we have the expression:

Since the transmissions at different wavelengths are the functions of the number of particles in aggregates or particle size, the transmission at one wavelength can be expressed as a parametric function of the transmission at another wavelength. This function is a straight line with reasonable accuracy. This conclusion is verified for both the transmissions themselves and the logarithms of transmission for different models and different simulations of erythrocyte shape.

If the transmission signal $T_1(t)$ is measured when using the incident wavelength λ_1 , and the transmission signal $T_2(t)$ is measured when using the incident wavelength λ_2 , then the slope of the line $T_1(\lambda_1)/T_2(\lambda_2)$ (or $\log T_1(\lambda_1)/\log T_2(\lambda_2)$) is a certain parameter, called "parametric slope" (PS) for a specific patient that can be determined. By this, we can get rid of the explicit usage of the size of aggregates, i.e., the values that cannot be known from experiments *in vivo*.

The model of Rogoskin for spheres is used to obtain an approximate analytical expression of the parametric slope *PS*. It should however be noted that, for the cases of more complicated shapes, the proper generalization also may be done.

Thus, the following expression is used:

$$PS = \frac{(\partial T / \partial r)_{\lambda_2}}{(\partial T / \partial r)_{\lambda_1}} = \frac{(\partial T / \partial \mu_{tr})_{\lambda_2}}{(\partial T / \partial \mu_{tr})_{\lambda_1}} \cdot \frac{(\partial \mu_{tr} / \partial r)_{\lambda_2}}{(\partial \mu_{tr} / \partial r)_{\lambda_1}}$$

wherein T is the transmission signal and μ_{tr} is the transport scattering coefficient that describes the energy decay for the case of anisotropic scattering, and is determined as follows: $\mu_{tr} = \mu_{scat}(1-g)$, g being the anisotropic coefficient.

Here, the case when $(\mu_{diff} \cdot d) \geq 1$ and $\sinh(\mu_{diff} \cdot d) \approx \exp(\mu_{diff} \cdot d)$ is used, wherein μ_{diff} is the diffusion coefficient; d is the thickness of the blood slab.

$$(\partial T / \partial \mu_{tr})_{\lambda} = - \langle H(\theta, 1) \rangle \cdot 3^{1/2} \cdot (1/2) \cdot (\mu_{abs} / \mu_{tr}) \cdot [d + (1 / \mu_{diff}) \cdot (1 + 2(\mu_{abs} / \mu_{tr}))] \cdot \exp(-\mu_d$$

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The derivative $(d\mu_{tr}/dr)_\lambda$ is got from the above expression for the scattering coefficient μ_{scat} for the sphere-based model.

The following expression is known:

$$(\partial\mu_{tr}/\partial r)_\lambda = -(3/2) \cdot (1/r^2) \cdot [K(\omega) - \omega \cdot K'(\omega)] \cdot H(1-H) \cdot (1-g)$$

5

wherein g is the average cosine of the scattering angle ($g = \langle \cos\theta \rangle$) and is connected with the anisotropy of the radiation scattering.

In the region of real value of parameters $1 < \omega < 2$, there is the approximation $K(\omega) \approx 0.82053 \cdot \omega + 0.0366$. Then, we have:

$$(\partial\mu_{tr}/\partial r)_\lambda = -(3/2) \cdot (1/r^2) \cdot 0.0366 \cdot H(1-H) \cdot (1-g)$$

10

The above ratio $(d\mu_{tr}/dr)_\lambda$ depends on the wavelength through the factor $(1-g)$ only.

The value μ_{tr} with $K(\omega) \approx 0.82053 \cdot \omega$ becomes:

$$\mu_{tr} \approx (3/2) \cdot 0.82053 \cdot 2 \cdot \pi \cdot (1/\lambda) \cdot H \cdot (1-H) \cdot (1-g)$$

15

If we substitute this expression in the above equations for $(dT/d\mu_{tr})_\lambda$, we receive the expression that depends on the wavelength very simply and does not depend on the size of particles.

As the result of substitution of μ_{tr} and $(d\mu_{tr}/dr)_\lambda$ in the above expression for PS , we receive the parameter that does not depend on the particle size.

20

Now we shall describe how the above theoretical considerations can be used in practice. What we actually obtained through the above simulations, is the fact that there exist a parameter ("parametric slope"), which does not depend on the particle size and only on the concentration of hematocrit in blood. This fact can be used for determining the concentration of a substance of interest in blood.

25

To do this, first, a set of calibration curves should be provided. Each calibration curve corresponds to a specific substance and is in the form of a

calibration curve is shown in Fig. 6b. By using this curve, the concentration of hemoglobin can be determined for the specific patient, to whom the measurements are applied.

Turning now to Figs. 7a and 7b, there are illustrated two steps in the method
5 for determining the concentration of glucose. Here, the wavelengths λ_1 and λ_2 are selected in the ranges 600-1300nm and 1500-1600nm, respectively, namely $\lambda_1=660\text{nm}$ and $\lambda_2=1550\text{nm}$. Fig. 7a illustrates the corresponding transmission signals as the functions of time, i.e., $T_1(t)$ and $T_2(t)$. Then, the function $\log T_2$ vs. $\log T_1$ is determined, as graphically illustrated in Fig. 7b, and the corresponding
10 parametric slope is determined as described above. Having determined the parametric slope value for a specific patient, a corresponding calibration curve (not shown) is used for determining the glucose concentration for this specific patient.

Another important blood parameter that can be determined with the invented method is the oxygen saturation in the patient's blood. Oxygen saturation is defined
15 as the ratio of the content of oxyhemoglobin (HbO_2) to the total amount of hemoglobin (Hb) in the blood volume unit. The classic pulse oximetry method allows for determining the oxygen saturation. This method utilizes the so-called "natural pulsatile" component of a light transmission signal. This pure natural pulse-related signal component of a detected signal, determined by an appropriate
20 signal processing technique, is commonly called the "AC component" of the detected signal, whereas the entire transmission signal by itself is called the "DC component" of the detected signal. The transmission measurements in the pulse oximetry are carried out simultaneously at two different wavelengths, for example $\lambda_1=760\text{nm}$ and $\lambda_2=940\text{nm}$, where the significant difference in the light absorption
25 of oxyhemoglobin and hemoglobin exists between the two chosen wavelengths. Two pairs of AC and DC components are obtained. Generally, the ratio R , defined as $(\text{AC/DC})_{\lambda_1}/(\text{AC/DC})_{\lambda_2}$, is the value of oxygen saturation.

We applied the "parametric slope" concept and obtained the same results as with the pulse oximetry technique. Fig. 8a illustrates two graphs P_1 and P_2 (the
30 provision of only one of them being sufficient for the purposes of the present

example, and for each time interval Δt a pair of parametric slope values is obtained from the following: $(\log T)_{\lambda_3}$ vs. $(\log T)_{\lambda_2}$ and $(\log T)_{\lambda_1}$ vs. $(\log T)_{\lambda_2}$. In other words, each point in the graph P' corresponds to a pair of parametric slopes calculated for a pair of wavelengths λ_3 - λ_2 and λ_1 - λ_2 , respectively, each for a corresponding one of the time intervals Δt . Each such parametric slope is determined in the above-described manner. The MegaSlope is determined as $\text{tg}(\varphi)$. A calibration curve shown in Fig. 9b presents the MegaSlope as the function of hemoglobin concentration, i.e., MS(H).

One more important feature of the present invention consists of determining the Erythrocyte Aggregation Rate (EAR) for a specific patient. Assuming that the only process that takes place at the state of the blood flow cessation is the erythrocytes' aggregation, the EAR can be simply determined as the rate of the time changes of light response signal, i.e., $\Delta T/\Delta t$ (or $\Delta \log T/\Delta t$). To this end, the transmission as the function of time is measured with one wavelength of incident radiation. For more precise measurements, two such transmission signals as functions of time are measured with two different wavelengths of incident radiation. As for the time interval Δt , it may be either initial time interval or asymptotic time interval. The EAR parameter can be used for the determination of such an important parameter as Erythrocyte Sedimentation Rate (ESR). This is illustrated in Fig. 10, showing the EAR ($\Delta \log T/\Delta t$) as the function of ESR, the latter being measured in the conventional *in vitro* manner.

Thus, the advantages of the present invention are self-evident. We have proved that the main effect defining the optical characteristics of blood in the state of temporarily blood flow cessation is the erythrocytes' aggregation. In other words, in the asymptotic time interval, the erythrocyte serves as the sensor for the determination of the various blood parameters. The technique of the present invention, preferably performed in a non-invasive manner, but even in an invasive manner, is simpler and quicker than the conventional one. A physician can apply this technique to evaluate the various blood conditions of a patient, and then, if desired, direct him to a laboratory for more careful measurements. The parameter

CLAIMS:

1. A method of optical measurements of at least one desired parameter of the patient's blood, the method comprising the steps of:
 - providing a state of blood flow cessation of the patient's blood within a measurement region, and maintaining the blood-flow cessation state during a predetermined time period;
 - performing measurement sessions within said predetermined time period, each measurement session including at least two measurements with different wavelengths of incident light, and obtaining measured data representative of the time dependence of light response of the blood in the measurement region;
 - analyzing the measured data for determining said at least one desired parameter, extracted from optical characteristics associated with erythrocytes aggregation process during the state of the blood flow cessation.
2. The method according to Claim 1, wherein said state of the blood flow cessation in the measurement region is provided by applying an occlusion mode to the patient's blood perfused fleshy medium.
3. The method according to Claim 2, wherein the application of the occlusion mode comprises the application of over-systolic pressure to the patient's blood perfused fleshy medium at a location upstream of said measurements region with respect to the direction of the normal blood flow in the patient's body.
4. The method according to Claim 3, and also comprising the step of preliminary optical measurements for detecting the existence of the blood flow cessation state.
5. The method according to Claim 2, wherein said predetermined period of time is insufficient for irreversible changes to occur in the fleshy medium.
6. The method according to Claim 5, wherein said predetermined period of time is from one second to several minutes.

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wherein n_{Hb} is the refraction index of hemoglobin in erythrocyte, and n_{pl} is the refraction index of plasma.

13. The method according to Claim 12, wherein the evaluation of the parameter $(n_{\text{Hb}} - n_{\text{pl}})$ comprises the utilization of theoretical data representative of a scattering function $K(x(n_{\text{Hb}} - n_{\text{pl}}))$, wherein $x = 2\pi a / \lambda$, a being the effective size of erythrocyte.

14. The method according to Claim 1, wherein the analyzing of the measured data comprises the steps of:

- determining a parametric slope, said at least two wavelengths being selected in accordance with said desired parameter to be determined; and
- using reference data in the form of a calibration curve of the parametric slope as a function of values of the desired parameter.

15. The method according to Claim 14, wherein the determination of the parametric slope comprises the determination of a function $T_{\lambda 2}(T_{\lambda 1})$, wherein $T_{\lambda 2}$ and $T_{\lambda 1}$ are the measured data corresponding to the wavelengths λ_2 and λ_1 of the incident radiation, respectively, the function $T_{\lambda 2}(T_{\lambda 1})$ being determined for a preset time interval of said predetermined time period.

16. The method according to Claim 14, wherein the determination of the parametric slope comprises the determination of a function $\log T_{\lambda 2}(\log T_{\lambda 1})$, wherein $T_{\lambda 2}$ and $T_{\lambda 1}$ are the measured data corresponding to the wavelengths λ_2 and λ_1 of the incident radiation, respectively, the function $T_{\lambda 2}(T_{\lambda 1})$ being determined for a preset time interval of said predetermined time period.

17. The method according to Claim 15 or 16, wherein said preset time interval is an initial time interval characterized by relatively strong changes of the light response signal with time, as compared to a next, asymptotic time interval of said predetermined period of time.

18. The method according to Claim 15 or 16, wherein said preset time interval is an asymptotic time interval characterized by relatively slow changes of the light response signal with time, as compared to an initial time interval of said predetermined period of time.

31. The method according to Claim 29, wherein Δt is an asymptotic time interval of the predetermined period of time characterized by relatively slow changes of the light response signal with time, as compared to an initial time interval of said predetermined period of time.

5 32. A method of optical measurements of desired parameters of the patient's blood extracted from optical characteristics associated with erythrocytes aggregation process during the state of the blood flow cessation, the method comprising the steps of:

- providing the state of the blood flow cessation within a measurement
10 region, and maintaining the blood-flow cessation state during a predetermined time period;
- performing measurement sessions within said predetermined time period, each measurement session including at least two measurements with different wavelengths of incident light, and obtaining measured
15 data representative of the time dependence of light response of the blood in the measurement region;
- analyzing the measured data for determining said at least one desired parameter, by determining at least one parametric slope value and a Rouleaux Geometry Factor (RGF) for said patient, the RGF
20 characterizing the changes of the light response of blood at the state of the blood flow cessation as the function of time and wavelengths of the incident radiation, associated with the erythrocytes' aggregation.

33. A method of optical measurements of at least one desired parameter of blood of a specific patient extracted from optical characteristics associated with
25 erythrocytes aggregation process during the state of the blood flow cessation, the method comprising the steps of:

- providing reference data in the form of a function describing diffraction effects on particles, $K(x(n_{Hb}-n_{H2O}))$, wherein $x=2\pi a/\lambda$; a is the size of erythrocyte, n_{Hb} is the refraction index of hemoglobin and n_{pl} is the
30 refraction index of water, λ is the wavelength of incident radiation;

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- using said calibration curve for determining the value of said desired parameter for said specific patient.

35. A measurement apparatus for performing non-invasive optical measurements of desired parameters of the patient's blood, the apparatus
5 comprising:

- an occlusion assembly for applying to the flow of the patient's blood, so as to create a state of the blood flow cessation in a measurement region for a predetermined time period;
- illumination/detection assembly for applying optical measurements with
10 at least two different wavelengths of incident radiation to said measurement region during said predetermined period of time, and generating data representative of light response signals; and
- a control unit responsive to the generated data for determining measured data in the form of time variations of the light response signals, for
15 utilizing optical characteristics associated with erythrocytes aggregation process during the state of the blood flow cessation to analyze the measured data from within a preset time interval of said predetermined period of time and determine the desired parameter of the patient's blood.

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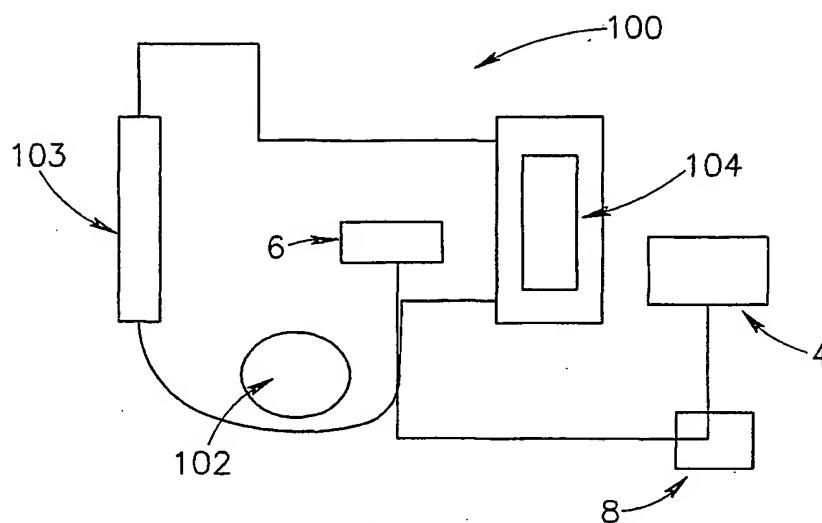


FIG.1B

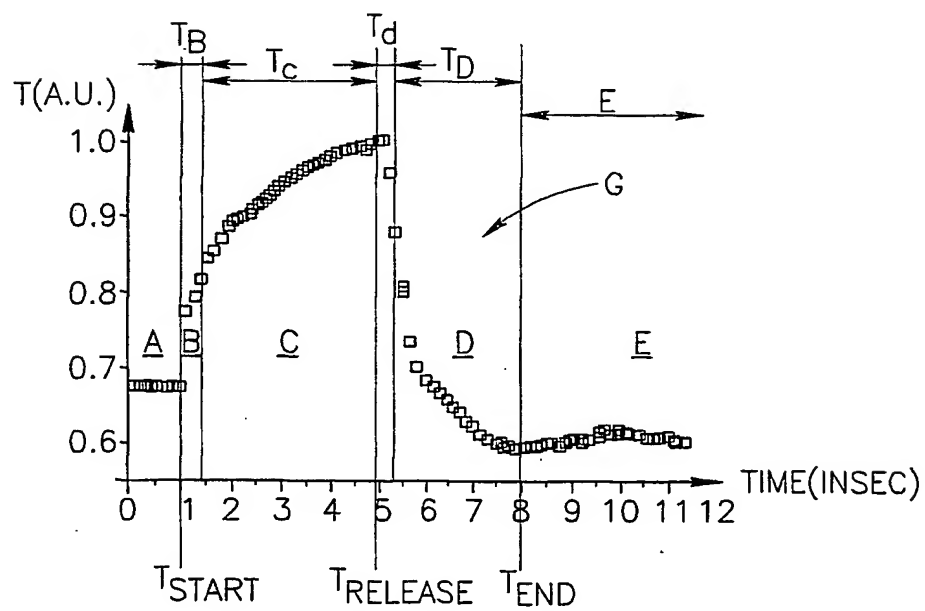


FIG.2

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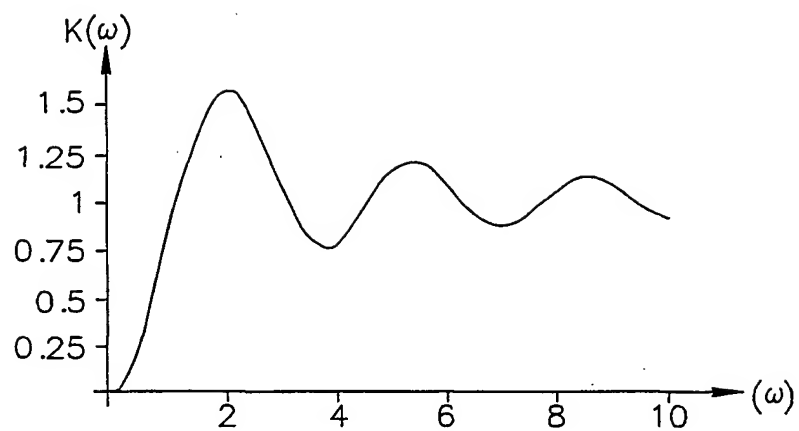


FIG.4A

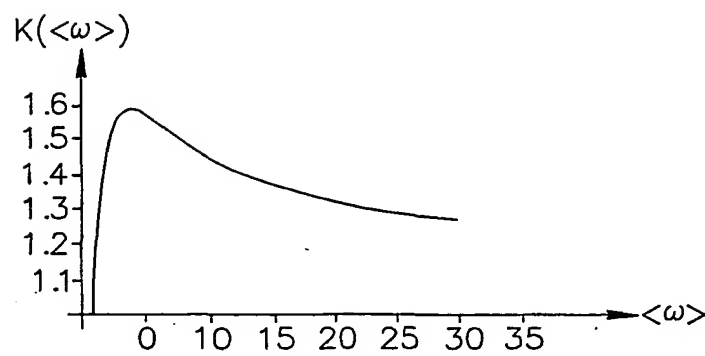


FIG.4B

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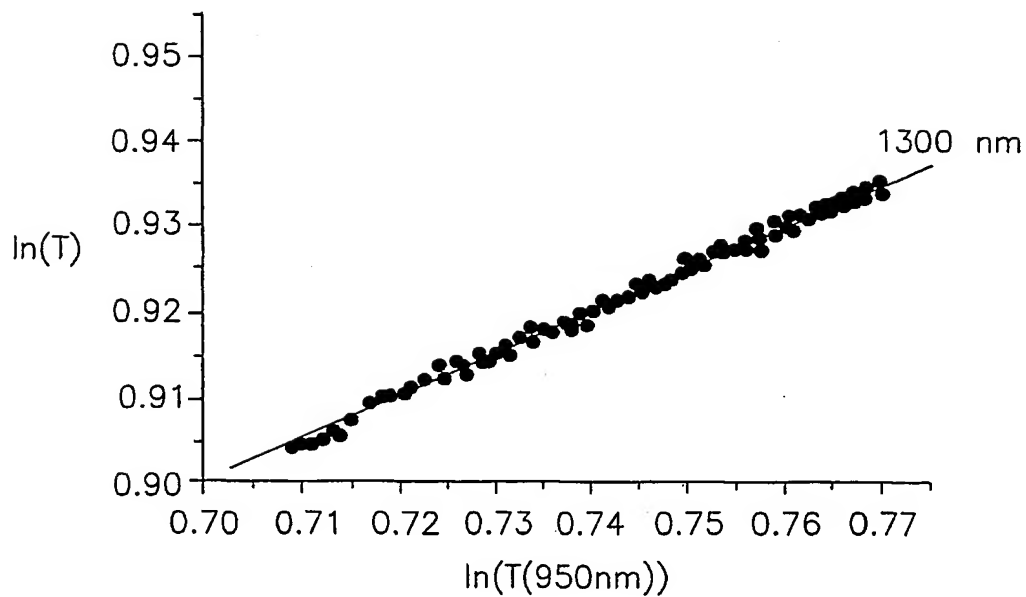


FIG.6A

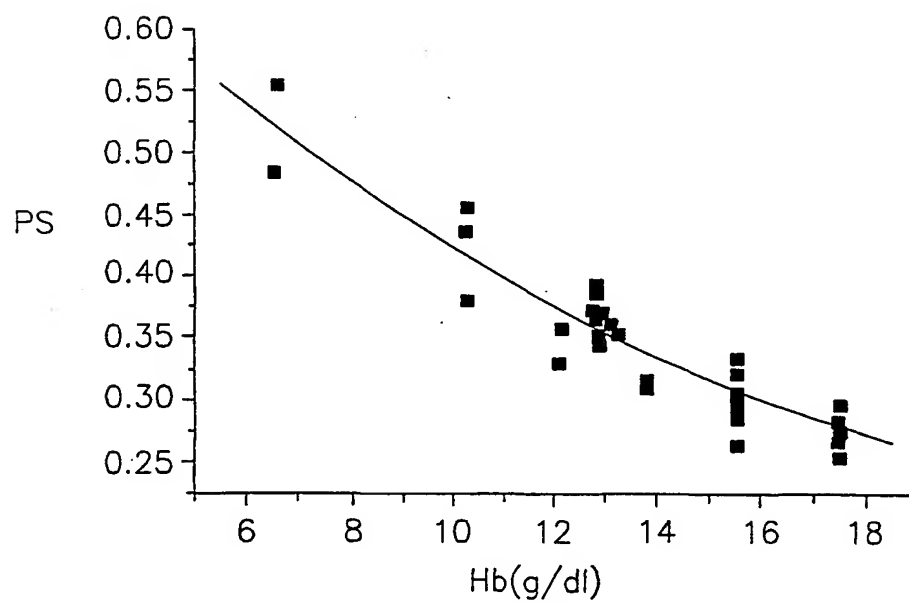
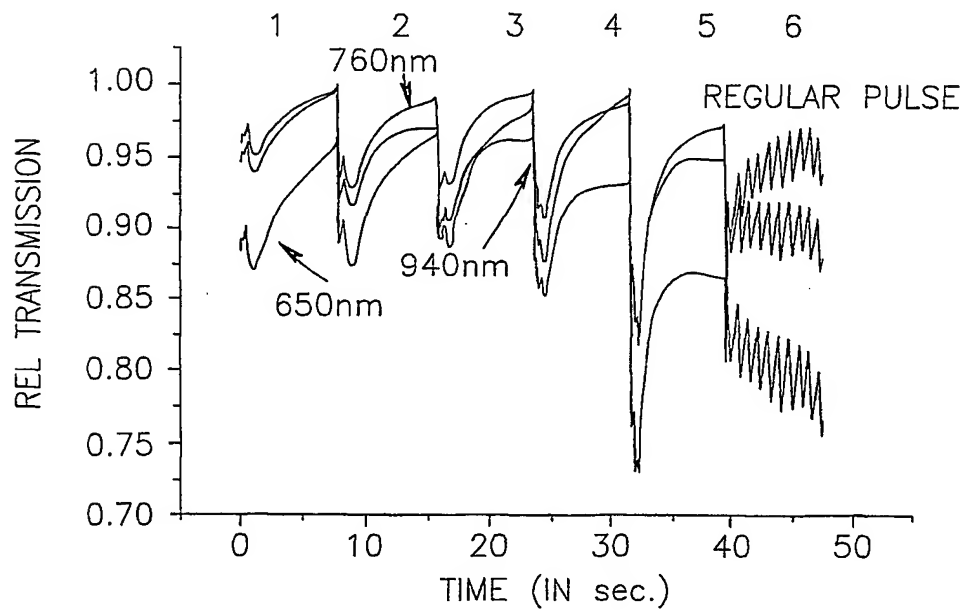
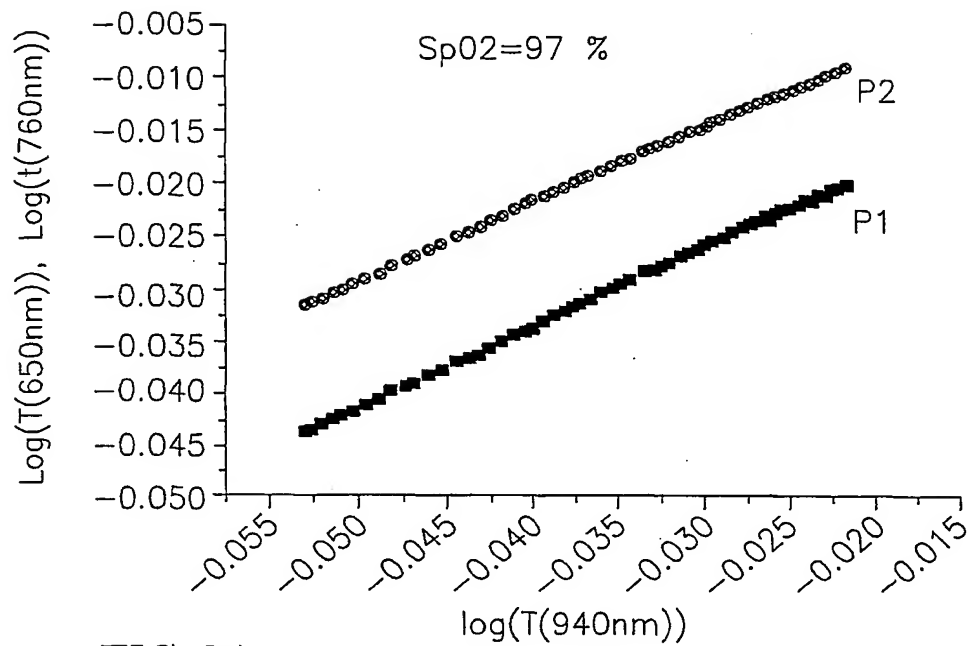


FIG.6B

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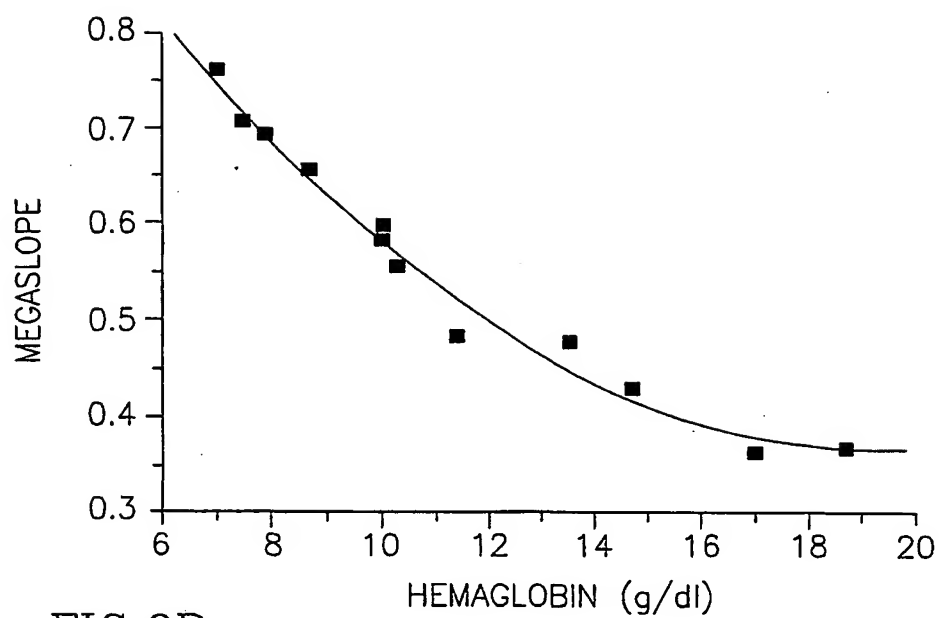


FIG.9B

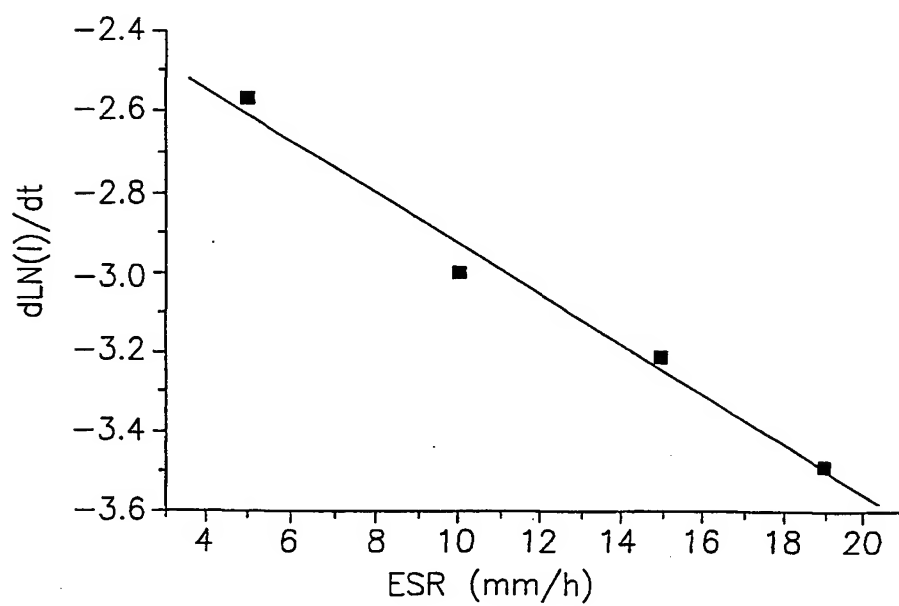


FIG.10

INTERNATIONAL SEARCH REPORT

Inter 1al Application No

PCT/IL 99/00694

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 17174 A (COOPER) 30 April 1998 (1998-04-30)	1,3,5,6, 14,19, 21,25, 26,28, 34,35 32,33
A	page 19, line 18 -page 38, line 3 -----	
X	US 4 463 762 A (RUBENS) 7 August 1984 (1984-08-07)	1-3,5,6, 14,19,35 32-34
A	column 2, line 13 -column 4, line 61 -----	